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# **Does physical inactivity increase personalised cardiovascular risk in males and females aged 40-80 years?**

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## **Abstract**

**Background** Various modifiable risk factors have been associated with increased risk of cardiovascular disease, with physical activity known to provide multiple health benefits, whilst inactivity is linked to increased prevalence of multiple cardiovascular risk factors.

**Objective** The aim of this study was to explore the association between physical activity level and personalised cardiovascular risk, in addition to the association between this risk behaviour and other modifiable cardiovascular risk factors.

**Method** Data was collected from 863 patients aged 40-80 years (54% male, aged  $62.18 \pm 12.35$  years) including, age, body mass index, blood pressure, total cholesterol and HDL cholesterol, smoking status, treatment for hypertension, presence of diabetes and personalised QRISK score.

**Results** Inactive patients had a statistically significant higher QRISK than those who were physically active and presented greater prevalence of multiple cardiovascular risk factors including diabetes, hypertension and obesity, in addition to negative health behaviours such as smoking. Males presented both statistically significant higher QRISK and prevalence of contributing risk factors.

**Conclusions** QRISK scores were significantly higher for those reported physically inactive. All other CV risk measures were higher and more prevalent in the inactive populations. All risk factors increased relative risk of the occurrence of high QRISK scores for both genders and males were at increased risk of all negative health behaviours and higher QRISK despite being more active.

**Key words:** Physical activity; cardiovascular disease; cardiovascular risk factors,

## **Introduction**

Cardiovascular disease (CVD) is a multifactoral condition reflecting a lifelong pathologic process. The population burden attributed to CVD has evolved rapidly in the UK and although genetic factors play a part in susceptibility, there is a strong body of evidence supporting the contention that specific lifestyle behaviours can increase the occurrence of otherwise modifiable risk factors (Luke *et al.*, 2011). The potential impact of primary health care in assessing and managing these particular risks, including physical inactivity, smoking, hazardous drinking and poor diet, is known to be particularly efficacious within high risk populations, via delivery of lifestyle advice and appropriate interventions (Harris, 2008). Physical inactivity is considered an important modifiable risk factor for CVD, with several studies and interventions reporting the protective effects and generally supporting the notion that regular activity lowers CVD markers and improves metabolic function (Dixon *et al.*, 2013).

## **Physical activity**

The protective mechanisms of physical activity (PA) include the regulation of body weight, reduction of insulin resistance, hypertension, atherogenic dyslipidaemia and inflammation and the enhancement of insulin sensitivity, glycemic control and fibrinolytic and endothelial function (Bassuk & Manson, 2005), which collectively can contribute to reduced CV risk. Current government guidelines recognise the importance of physically active behaviours, recommending adults engage in at least 150minutes of moderate-intensity exercise, or 75minutes of vigorous-intensity exercise each week. The Health Impact of Physical Inactivity survey (HIPI, 2013) shows in Cornwall, the prevalence of diabetes in those aged 40-79 could be reduced by 199 to 3,427 cases if 25-100% of this population was more active, yet majority of adults do not achieve the government recommendations. Levels of PA required to produce protective effects and extend life expectancy were investigated in a cohort study of adult populations, comparing health benefits from a range of PA volumes along with hazard ratios for mortality risks and life expectancy (Wen *et al.*, 2011). Conclusions infer that compared to inactive groups, even those partaking in low-volumes of activity, equivalent to 15-minutes per day, produced a 14% reduced risk and every additional 15-minutes a day, further reduced all-cause mortality by 4%. These benefits were applicable to both sexes of all age groups and those with current CV risks.

Hu *et al.*, (2004) found middle-aged women who were reported to be inactive, experienced a doubling of CV related mortality and these relative risks were similar to those for hypertension and smoking. Studies that include both male and female participants also suggest an inverse association between PA and many CV risk factors. Moe *et al.*, (2013) found diabetes to be associated with nearly threefold higher CV risk if patients were reported physically inactive. Risk of CVD mortality was significantly lower if participants were moderate to vigorously active, compared with inactive counterparts, suggesting higher levels of physical activity offer the potential to lower risk of CVD mortality. PA has been reported as equally or perhaps more important than pharmacotherapy for reducing the risk of mortality in adults with hypertension, despite an already increased risk for hypertensive compared with

normotensive populations, therefore, endorsing the potential therapeutic effects of exercise (Brown *et al.*, 2013). Associations have also been formed with CV risk factors such as inflammatory markers, linked to the mechanisms underlying atherosclerosis. Ahmed *et al.*, (2012) found PA correlated with triglyceride reduction and high-density lipoprotein (HDL) increase, again linking physical activity to CVD risk reduction.

### **Modifiable risk behaviours**

Considering combined and independent associations of modifiable risk factors, Hamer and Stamatakis (2008) explored health behaviours including smoking, excess alcohol intake, elevated cholesterol, obesity, raised blood pressure and a sedentary lifestyle on inflammation and homeostasis, based on levels of fibrinogen. A graded increase in risk was apparent with the accumulative number of modifiable risk factors, with central adiposity the strongest independent factor, although all except cholesterol and alcohol were independently associated to increased inflammation. Results also showed participants with higher numbers of risk factors were older. Despite several studies looking at associations between PA and individual CV risks, no study appears to investigate the associations of physical inactivity, combined with multiple other risk factors and their cumulative effects on personalised CV risk, particularly in older adults.

### **High risk populations**

It is well recognised that the population is aging and this will have significant economic and social impacts (McNaughton *et al.*, 2012). The prevalence of CVD accelerates significantly after the age of 40 (SEPHO, 2013) increasing markedly with age and can be 2 to 5 times more common in males (Jousilahti, *et al.*, 1998). In Cornwall, it is estimated that by 2030, the percentage of the population over 40 years will increase to 28.3% for males and 31.4% for females. While life expectancies are increasing, there is greater need to raise awareness of improved quality of life, requiring greater input from effective promotion of lifestyle change through general practice (Ashden *et al.*, 2013). Previous research concludes that PA levels decline sharply after 50 years of age, irrespective of current activity level and although males are reported to be more physically active, this occurs in both genders, supporting the need for intervention (Luke *et al.*, 2011).

Significant adverse trends in obesity and CV risk factors have increasingly emerged, with obese and overweight individuals known to be at greater risk of various metabolic markers and development of chronic diseases, as well as exhibiting more sedentary behaviours. However, only a third of overweight or obese patients are reported to have received lifestyle advice from a general practitioner (Booth & Nowson, 2010). It has been observed that in older adults, life transitions particularly retirement could influence weight gain and inactive behaviours, which can then negatively impact other aspects of health (Plotnikoff *et al.*, 2004). There is a need for primary care practitioners to recognise the prevalence of modifiable risk factors among adults, particularly those with accompanying conditions such as diabetes or hypertension. Becoming aware of patterns in which risk factors cluster, may improve

identification of high-risk patients, as co-occurrence has been linked to an accelerated CVD process.

### **Intervention**

Unhealthy lifestyle plays an influential role in the development of CVD and risk perceptions may aid informed, positive health decisions to improve lifestyle (Koelewijn-van Loon *et al.*, 2010). Individual perceptions surrounding the need to change are considered essential to achieve behaviour alterations and are shown to have a positive influence in facilitating PA behaviours (Vahasarja *et al.*, 2012). In agreement, a study by Egede and Zheng (2002) found that in adults with diabetes, despite an already higher prevalence of CV risk, strategies such as counseling with focus on controlling and reducing risk factors such as smoking, obesity and physical inactivity have beneficial effects. Ultimately, a pro-active approach to health promotion is required, allowing for early detection of ill-health behaviours and more importantly, early detection of negative behaviour clusters, to facilitate cost effective preventative interventions, opposed to treatment and management. The prevailing view within scientific literature is that more active individuals tend to develop fewer risk factors, display lower prevalence of CVD than sedentary counterparts and if cardiovascular health does diminish it occurs at a later age and lesser severity (Myers, 2003). Detecting and managing high risk behaviours can facilitate sustained change at a sufficient level to result in measurable improvements to public health. Therefore, it is vital to encourage general practitioners to actively promote and educate patients on positive lifestyle behaviours (Bassuk & Manson, 2005).

Asymptomatic patients at high risk of CVD need to be identified, to enable advice to be appropriately prescribed. As there are numerous markers that contribute to CV risk, equations developed from the Framingham Cohort Study have developed a 10-year CVD risk algorithm (QRISK). The complex modeling techniques of QRISK considers traditional risk factors such as age, sex, cholesterol/HDL ratio, blood pressure, diabetes, smoking status, ethnicity, family history, deprivation, blood pressure treatment, body mass index, rheumatoid arthritis, chronic kidney disease and atrial fibrillation. However, factors known to increase CVD risk such as physical inactivity are not directly accounted for. The aim of this study was therefore, to investigate the association between physical activity level and personalised CV risk (QRISK) in adults 40-80 years. Considering the accumulative effects of modifiable risk factors linked to physical inactivity, this study also aimed to establish if these combined negative health behaviours had a direct impact on increased QRISK scores.

### **Methodology**

#### **Design**

The current study was designed to evaluate the effects of PA level on 10-year CVD risk in patients 40-80 years old, by reviewing existing patient data at Penryn Surgery. Two searches were conducted using the Clinical Reporting tool on GP System One. Search criteria were firstly input for QRISK scores,

using Read code Y0a8a, which denotes a computer calculated risk assessment attached to individual patients clinical journals. A second search was input for all four General Practice Physical Activity Questionnaire (GPPAQ) outcome Read codes, active (XaPPE), moderately active (XaPPD), moderately inactive (XaPPB) and inactive (XaPP8). The two clinical reports were then merged to leave only those patients matching both searches inclusion criteria. Age adjustments were made, presenting only data of patients 40-80 years and then split into four groups based on activity Readcodes. From each of the four groups, QRISK score (%), gender, age, BMI (then converted to weight classification), blood pressure, cholesterol, HDL cholesterol, smoking status, current treatment for hypertension and presence of diabetes were recorded for each patient. Data collection took place over a two-week period at Penryn Surgery and data collected from System One was checked by a supervising GP before transferring to the external data analysis programme.

### **Participants**

The study was a population-based analysis of general practice electronic data and no identifiable patient data was used. Clinical reports were created from patients actively registered at the Penryn Surgery, with a current patient database of 17,647. Provided patients had both QRISK and GPPAQ Readcodes and were 40-80 years of age, there were no other health indicators or criteria for exclusion, ensuring the sample would infer to the practice population increasing external validity of results and ensuring no bias data was created using subject specific selection.

### **QRISK**

Derived from equations from the American Framingham Cohort Study (Hippisley-Cox *et al.*, 2007), QRISK calculates cardiovascular risk based on risk factors such as age, sex, cholesterol/HDL ratio, blood pressure, diabetes and smoking status. In addition, QRISK takes in to account additional factors known to affect individual risk of developing heart disease, such as ethnicity, family history, deprivation (using the town's deprivation score), blood pressure treatments, BMI, rheumatoid arthritis, chronic kidney disease and atrial fibrillation. As cardiovascular risk is closely associated with socio-economic status, four variables obtained from census data based on postcode: unemployment, overcrowding, lack of owner occupied accommodation and lack of car ownership, all equate to scores considered the best indicator of material deprivation and this is used in QRISK calculations by inclusion of a practice deprivation score.

### **Physical activity level**

The Department of Health's General Practice Physical Activity Questionnaire (GPPAQ) is a validated tool used by primary care practitioners to identify inactive individuals. A 4-level Physical Activity Index reflecting an individual's current level of physical activity is completed electronically on System One during NHS health checks, with outcomes then cross-referred to Read codes. GPPAQ is entered on the clinical records and updated at least every 5-years and patients with clinical evidence of 10-year QRISK greater than 30% should have GPPAQ recorded annually.

### **Measurements of risk factors**

Data on high risk factors were drawn from the QRISK calculation template.

*QRISK*- In the United Kingdom the National Institute for Health and Clinical Excellence refers to a 10-year cardiovascular disease risk of >20% as high risk.

*Physical activity*- Inactive patients were considered high risk

*BMI classification*- Obese patients ( $BMI \geq 30$ ) were considered high risk

*Smoking status*- High risk was defined as current smoker

*Diabetes*- All diabetics were high risk, regardless of Type 1 or Type 2

*Hypertension*- Patients treated for hypertension were considered high risk

*Cholesterol*- Patients with total cholesterol  $\geq 5.1$ mmol/L were considered high risk

### **Statistical methods**

SPSS for Apple Mac (Version 21) was used for the statistical analysis of data and descriptive statistics were used to describe the sample. Pearson's Chi Square tests were used to analyse differences between groups and for preliminary assessment of the associated factors, with One-way ANOVA used to analyse and compare mean values. As cardiovascular risk increases with age (>65y $\uparrow$ ) and gender is an influencing factor (males $\uparrow$  in those <65y) (Simon *et al.*, 2010), for greater validity of analysis and to ensure results represented detailed findings that were age and gender specific, data was split for analysis in to four sub-groups: females 40-64years, females 65-80years, males 40-64years and males 65-80years. Pearson's bivariate correlation was used to establish associations between QRISK and each independent variable and Binary Logistic Regression was completed to depict odds ratios and predict each independent variables contribution to variations in QRISK scores.

### **Ethical consideration**

The Penryn Surgery gave written consent for data collection from the GP System One database, due to the use of non-identifiable data for population evaluation purposes. Ethical approval was then granted from the Science and Environmental Ethics Committee at Plymouth University. As no contact was made with and patients, nor records or identifiable data accessed, informed consent was not required from the participants and NHS ethical approval was not required.

### **Results**

A total of 935 patients were in the combined search matching both inclusion criteria and when adjustments were made for age, final patient count was 863. The sample was fairly small in comparison to practice size, due to recording of GPPAQ Read codes to clinical records being a fairly new protocol, for patients seen in the NHS Health Check clinics. Mean age of patients was  $62.18 \pm 12.35$  and once adjustments were made for age, 466 males aged  $62.91 \pm 11.59$  and 397 females aged  $61.31 \pm 13.15$ , were split between the four physical activity groups: active ( $n=163$ ), moderately active ( $n=135$ ), moderately inactive ( $n=111$ ) and inactive ( $n=454$ ). Males constituted 54% of total data and within physical activity groups, gender contributions were similar, with slightly larger number of males in each group, shown in Table 1. QRISK as a population value was  $20.51 \pm 14.70$  %. BMI as a population value

was  $28.92 \pm 5.61 \text{ kg/m}^2$ . Of the total population, 40% were overweight and 36.2% obese, with just 22.2% of the population presenting a normal weight and 1.6% underweight. Prevalence of CV risk factors for the population presented 42.1% with high cholesterol ( $\geq 5.1 \text{ mmol/L}$ ), 57.9% on treatment for hypertension, only 18.8% with diabetes, 12.6% current smokers although 41.6% were ex-smokers.

**Table 1:** Characteristics of participants

	All data	Active	Mod-Active	Mod-Inactive	Inactive
All participants	863	163	135	111	454
Gender <i>n</i> (%)					
Male	466 (54)	98 (60.1)	86 (63.7)	52 (46.8)	230 (50.7)
Female	397 (46)	65 (39.9)	49 (36.3)	59 (53.2)	224 (49.3)
Age (years)	$62.18 \pm 12.35$	$54.56 \pm 11.89$	$57.67 \pm 12.14$	$56.78 \pm 11.98$	$67.57 \pm 9.9$
40-64 <i>n</i> (%)	403 (46.7)	118 (72.4)	81 (60)	74 (66.7)	130 (28.6)
65-80 <i>n</i> (%)	460 (53.3)	45 (27.6)	54 (40)	37 (33.3)	324 (71.4)
BMI <i>n</i> (%)	$28.92 \pm 5.61$	$27.42 \pm 4.87$	$28.8 \pm 4.88$	$28.16 \pm 5.46$	$29.69 \pm 5.96$
20-24 $\text{kg/m}^2$	206 (23.9)	55 (33.7)	25 (18.5)	31 (27)	95 (20.9)
25-29 $\text{kg/m}^2$	345 (40.9)	65 (40)	64 (47.4)	45 (31.5)	171 (37.7)
$\geq 30 \text{ kg/m}^2$	312 (36.2)	43 (26.3)	46 (34.1)	35 (31.5)	188 (41.4)
BP <i>n</i> (%)	$131.73 \pm 15.73$	$128.90 \pm 15.21$	$129.85 \pm 14.09$	$130.88 \pm 18.59$	$133.50 \pm 15.43$
<120 mm Hg	187 (21.6)	44 (27)	32 (23.7)	28 (25.2)	83 (18.3)
120-139 mm Hg	419 (48.6)	83 (51)	74 (55.6)	51 (45.9)	211 (46.5)
$\geq 140 \text{ mm Hg}$	257 (29.8)	36 (22)	29 (20.7)	32 (28.9)	160 (35.2)
Cholesterol <i>n</i> (%)	$5.06 \pm 1.68$	$5.07 \pm 1.06$	$5.12 \pm 1.13$	$5.16 \pm 1.15$	$5.01 \pm 2.07$
<5.1 mmol/L	467 (57.9)	85 (52.1)	71 (52.6)	57 (51.4)	253 (57.8)
$\geq 5.1 \text{ mmol/L}$	387 (42.1)	78 (47.9)	64 (47.4)	54 (48.6)	387 (42.2)
HDL	$1.65 \pm 5.06$	$1.49 \pm 0.49$	$1.48 \pm 0.48$	$1.46 \pm 0.39$	$1.18 \pm 6.98$
QRISK <i>n</i> (%)	$20.51 \pm 14.70$	$12.25 \pm 11.14$	$15.50 \pm 12.29$	$14.05 \pm 12.01$	$26.53 \pm 14.42$
<20%	449 (52)	129 (79.1)	90 (66.7)	78 (70.3)	152 (33.5)
$\geq 20\%$	414 (48)	34 (20.9)	45 (33.3)	33 (29.7)	302 (66.5)
Hypertensive <i>n</i> (%)					
Yes	500 (57.9)	65 (39.9)	74 (54.8)	55 (49.5)	306 (67.4)
No	363 (42.1)	98 (60.1)	61 (45.2)	56 (50.5)	148 (32.6)
Diabetic <i>n</i> (%)					
Yes	162 (18.8)	21 (12.9)	15 (11.1)	19 (17.1)	107 (23.6)
No	701 (81.2)	142 (87.1)	120 (88.9)	92 (82.9)	347 (76.4)
Smoking Status <i>n</i> (%)					
Current smoker	109 (12.6)	17 (10.4)	15 (11.1)	16 (14.1)	61 (13.4)
Non-Smoker	395 (45.8)	87 (54.4)	59 (43.7)	54 (86.7)	195 (42)
Ex-smoker	353 (41.6)	59 (36.2)	61 (45.2)	41 (36.9)	198 (43.6)



### Gender and risk factors

Table 2 displays the gender distribution across each activity group with males contributing greater numbers to the two active groups (60.1% and 63.7%) compared with inactive groups (46.8% and 50.7%). Males and females contributed equally to overweight and obese classifications with no significant difference between genders ( $P=.068$ ). Smokers were more prevalent in males (16.1%) compared with females (8.6%) with a significant difference between genders ( $P<.0005$ ). Hypertension was not significantly different ( $P=.406$ ) between genders with over half the population of both genders hypertensive (male 59.2% and female 56.4%). Diabetes showed a significant difference ( $P=.028$ ) between genders with 61.7% of males and 38.3% of females diabetic. As continuous data, there was no significant difference between genders for cholesterol ( $p=.089$ ), but as categorical data, having high cholesterol showed a significant difference in genders ( $p<.0005$ ). QRISK was  $26.19 \pm 14.52$  in males and  $16.19 \pm 13.72$  in females with males presenting a statistically significant higher QRISK ( $p<.0005$ ).

**Table 2:** Distribution of age and gender within physical activity level

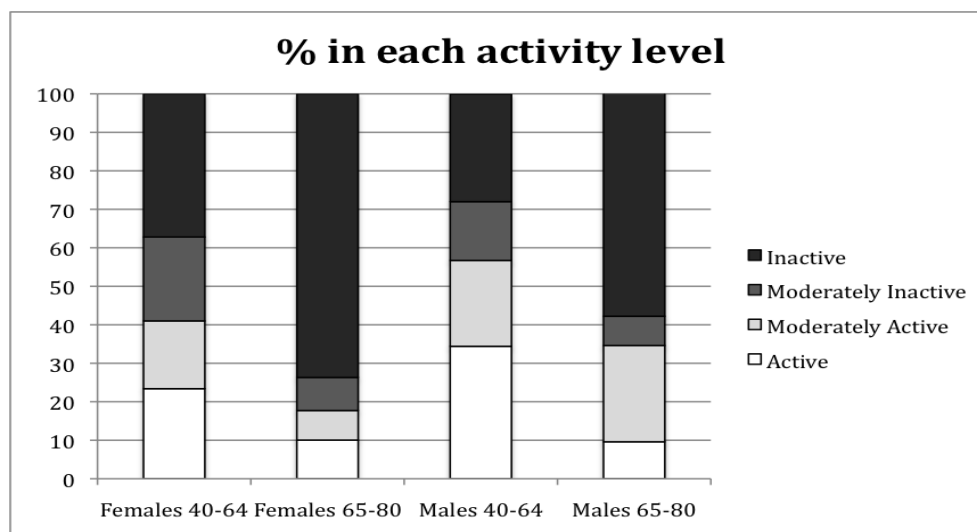
	<i>n</i> total	<i>n</i> F40-64	<i>n</i> F65-80	<i>n</i> (%)	<i>n</i> M40-64	<i>n</i> M65-80	<i>n</i> (%)
Active	163	44	21	39.9	74	24	60.1
Moderately Active	135	33	16	36.3	48	38	63.7
Moderately Inactive	111	41	18	53.2	33	19	46.8
Inactive	454	70	154	49.3	60	170	50.7

### Physical Activity Level

Pearson's Chi Square tests were used for comparing prevalence of risk factors associated to cardiovascular health between physical activity levels shown in Table 1. Of the total population ( $n=863$ ) 18.9% ( $n=163$ ) were reported active, 15.6% ( $n=135$ ) moderately active, 12.9% ( $n=111$ ) moderately inactive and 52.6% ( $n=454$ ) inactive. Figure 1 shows this heavily inactive population and its distribution through each gender and age group. In both males and females over 65 years inactivity significantly increases, and females 40-64 years were shown to be less active than males.

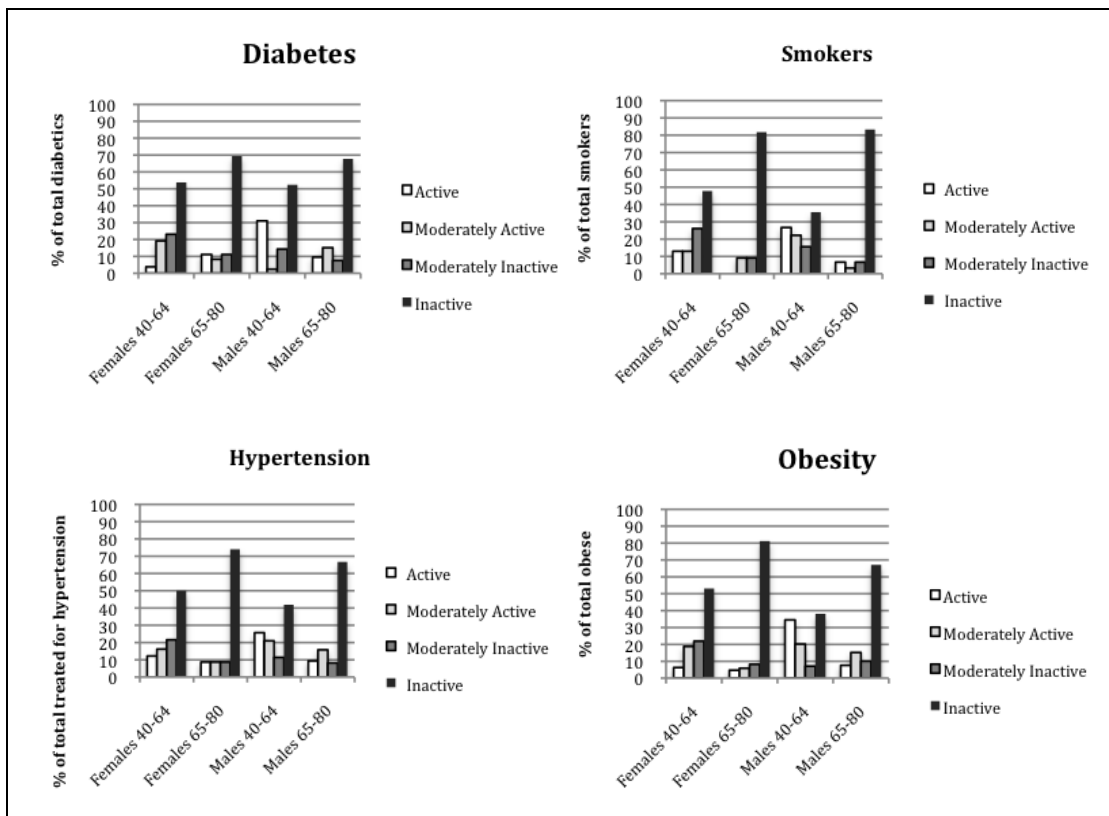
Cardiovascular risks within each physical activity group in the clinical report showed all diabetics comprised of 13% active, 9.3% moderately active, 11.7% moderately inactive and 66% inactive patients ( $f_{(.822)}=5.391$ ,  $p=.001$ ). Those on treatment for hypertension comprised of 13% active, 14.8% moderately active, 11% moderately inactive and 61.2% inactive patients ( $f_{(3.432)}=14.738$ ,  $p<.0005$ ). Smokers comprised of 15.6% active, 13.8% moderately active, 14.7% moderately inactive and 56% inactive patients ( $f_{(.349)}=.759$ ,  $p=.517$ ). Patients with high cholesterol comprised of 20.2% active, 16.5% moderately

active, 14% moderately inactive and 49.4% inactive patients ( $f_{(8.938)}=28.767$ ,  $p<.0005$ ).



**Figure 1:** Percentage of each age and gender group made up from all four activity level

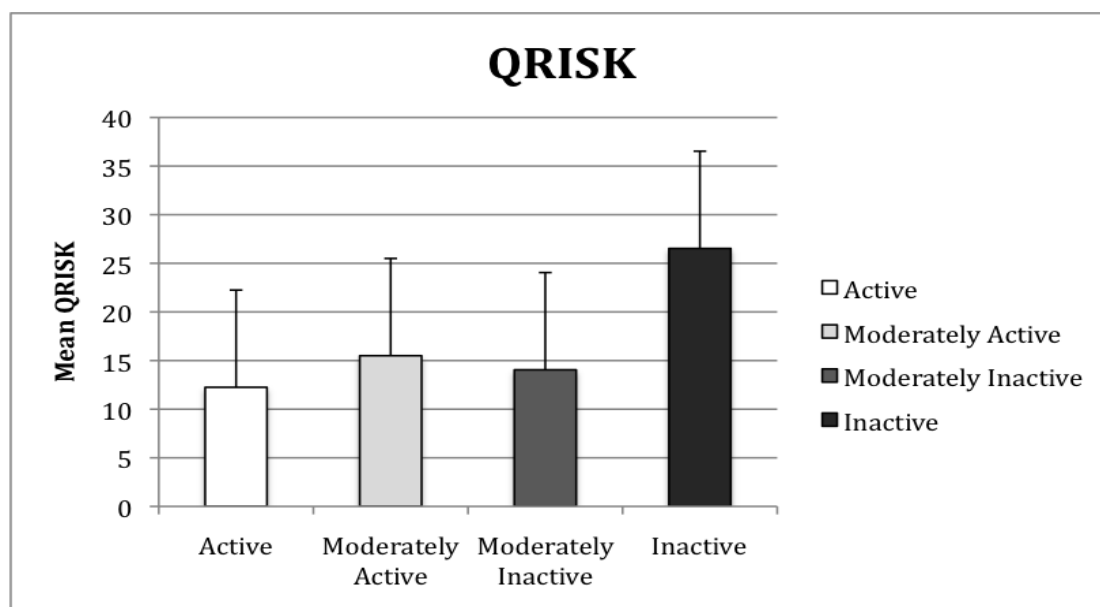
Overweight patients comprised of 18.8% active, 18.6% moderately active, 13% moderately inactive and 49.6% inactive and similarly obese patients comprised of 13.8% active, 14.7% moderately active, 11.2% moderately inactive and 60.3% inactive ( $f_{(3.414)}=5.431$ ,  $p=.001$ )(Figure 2).



**Figure 2:** Bar chart for modifiable risk factors diabetes, smoking, hypertension and obesity for all four physical activity levels

## QRISK

Analysis of all 863 patients data with One-Way-ANOVA showed a significant difference in QRISK between all activity levels ( $f_{(3,859)}=67.27$ ,  $p<.0005$ ) and comparison of means via an Independent-Samples T Test showed statistical significance between active/moderately active groups ( $p=.017$ ) and moderately inactive/inactive groups ( $p<.0005$ ), yet QRISK between moderately active and moderately inactive groups were not significant ( $p=.353$ ). Mean QRISK scores are shown in Figure 3. One-Way ANOVA used to establish differences in QRISK between all activity, gender and age groups, found a statistically significant difference in QRISK between all four activity levels for females 40-64yrs ( $f_{(3,184)}=7.801$ ,  $p<.0005$ ), males 40-64yrs ( $f_{(3,211)}=24.471$ ,  $p<.0005$ ) and males 65-80yrs ( $f_{(3,247)}=7.665$ ,  $p<.0005$ ). However, no significance was found between activity levels in females 65-80yrs ( $f_{(3,205)}=1.962$ ,  $p=0.121$ ). Distribution of QRISK scores for each activity group, age and gender can be seen in Figure 4.

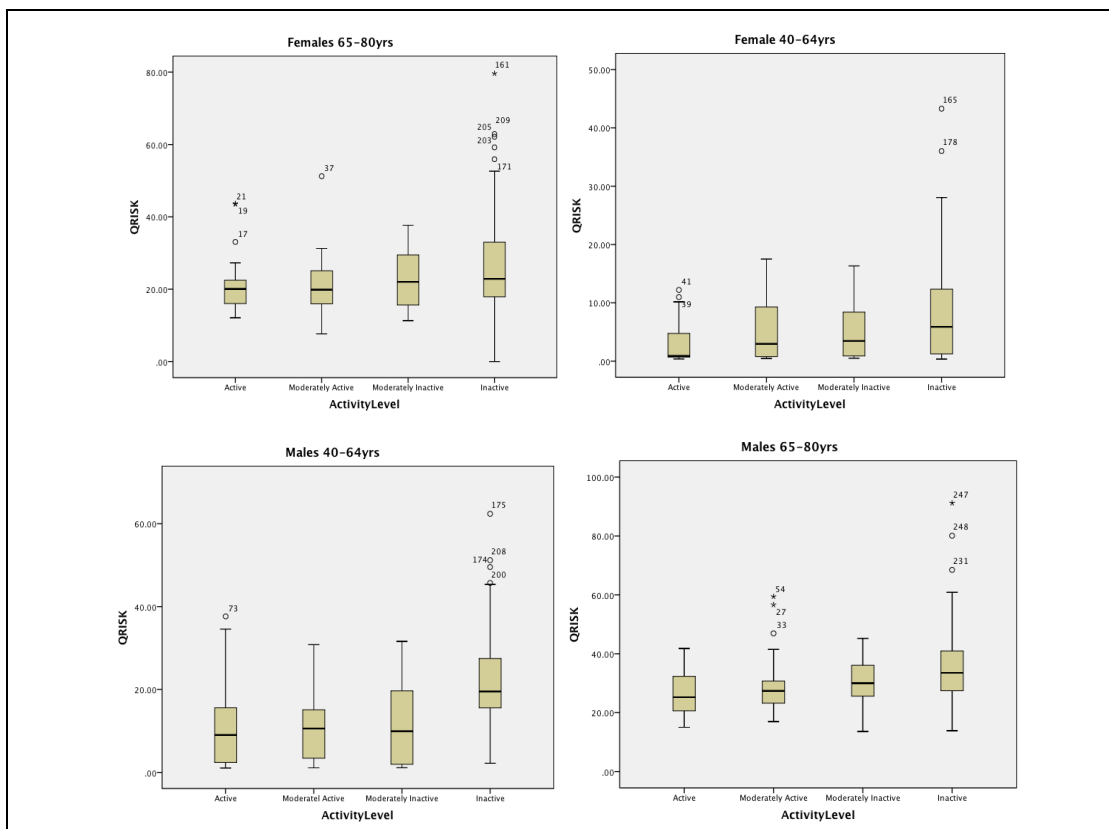


**Figure 3:** Bar chart showing mean QRISK scores in each activity level

\*Significant difference between active and moderately active ( $p=.017$ ), no significant difference between moderately active and moderately inactive ( $p=.857$ ) and significant difference between moderate inactive and inactive ( $p<.0005$ ).

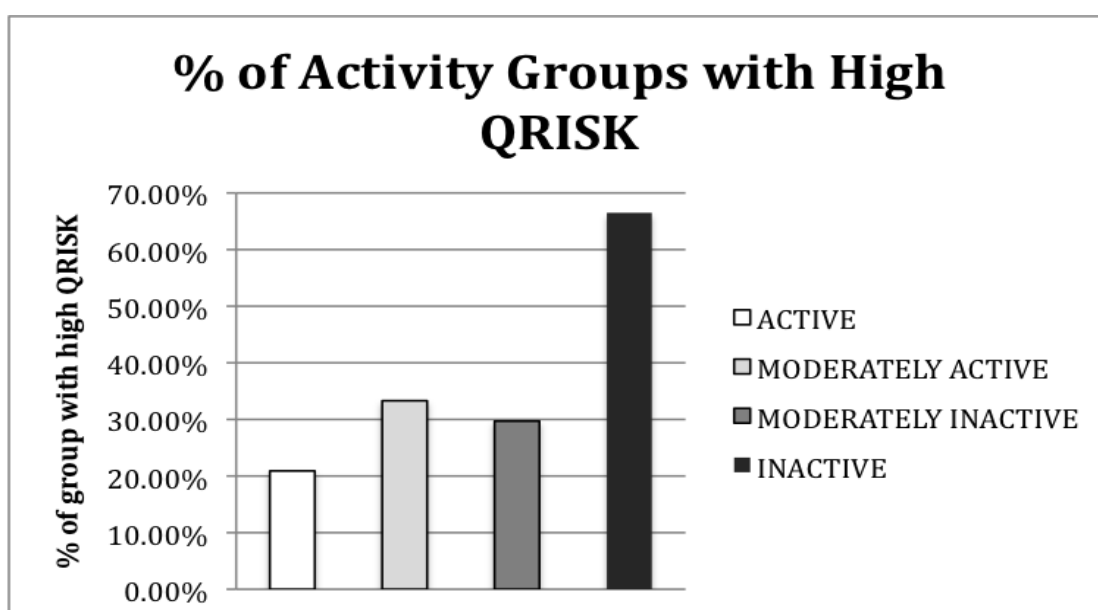
## High QRISK

Within the activity levels, patients considered to be high cardiovascular risk ( $\geq 20\%$ ) comprised of 21.5% active, 40% moderately active, 29.7% moderately inactive and 67.6% inactive. A significant difference was found for occurrence of high QRISK between activity levels ( $p<.0005$ ). This incremental trend was still apparent when broken down into age group and gender, with those inactive showing a significantly greater QRISK ( $p<.0005$ ). Irrespective of activity level, males presented a higher QRISK within each age group and complete data sample. Multiple comparisons with high QRISK as the dependent variable were carried out using Tukey HSD, showed a significant difference in presentation of high QRISK scores in the inactive group compared with each other activity level ( $p<.005$ ).

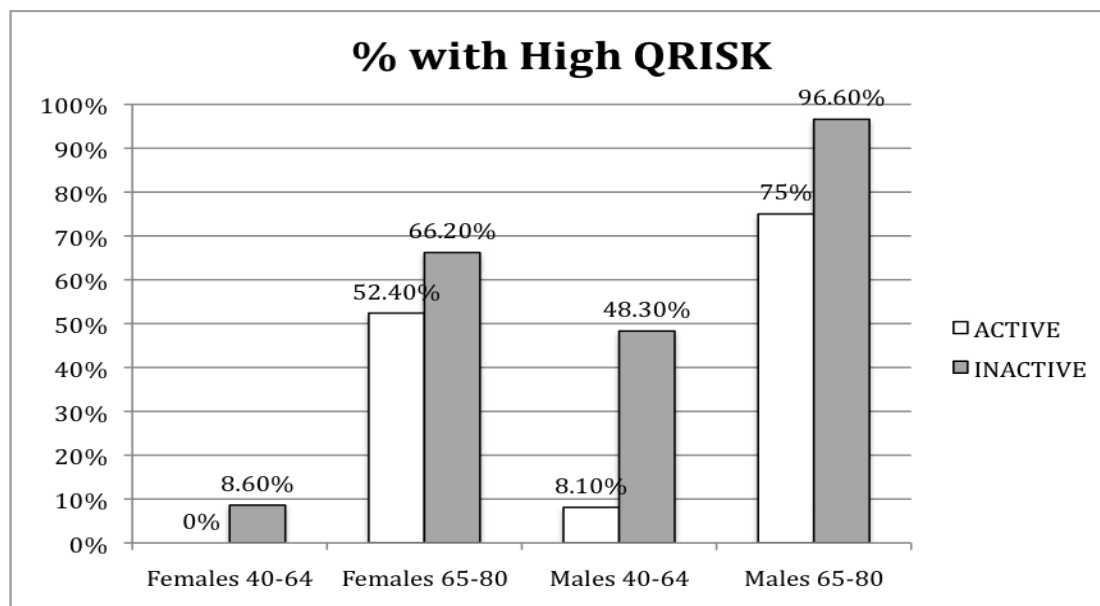


**Figure 4:** Steam and leaf plots for all four physical activity groups for each age and gender

However, between the moderate and active groups no significant difference was detected (Figure 5). Figure 6 shows the presentation of high QRISK scores for gender and age between active and inactive groups, displaying a significant difference between gender ( $p < .0005$ ) and activity level within gender ( $p < .005$ ).



**Figure 5:** Total percentage of patients with high QRISK scores ( $\geq 20\%$ ) within all four activity levels



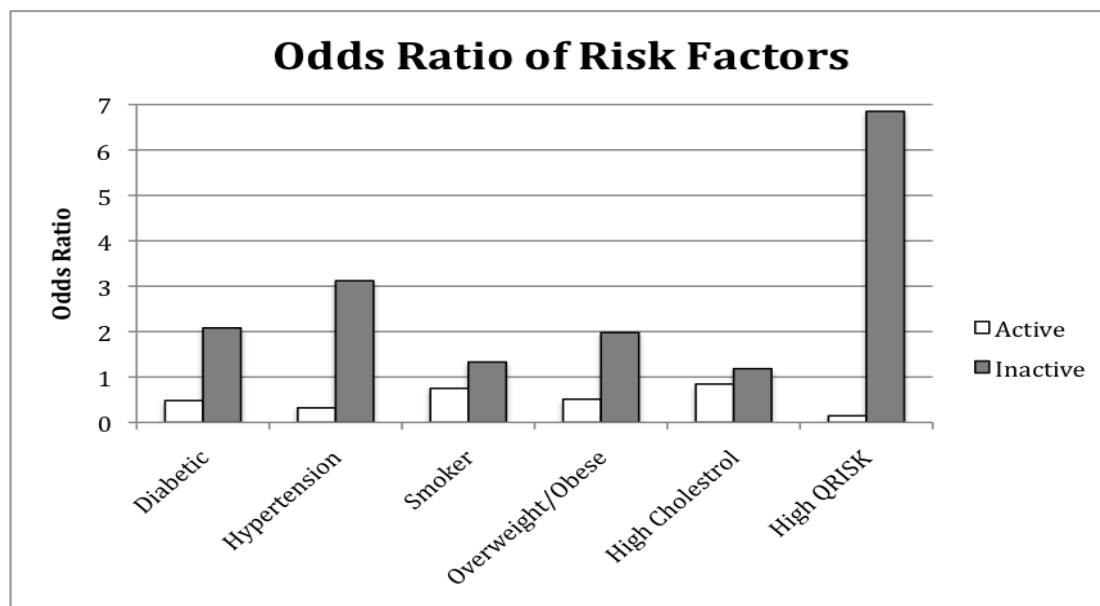
**Figure 6:** Total percentage of patients with high QRISK scores ( $\geq 20\%$ ) in active and inactive groups for all four age and gender groups

### Correlations

To establish the relationship of each individual risk factor with QRISK score Pearson's Bivariate correlation was calculated. Age ( $r=0.779$ ,  $n=863$ ,  $p<0.0005$ ), BMI ( $r=0.185$ ,  $n=863$ ,  $p<0.0005$ ), and BP ( $r=0.283$ ,  $n=863$ ,  $p<0.0005$ ) were all statistically significant but cholesterol was not significant ( $r=0.003$ ,  $n=863$ ,  $p=0.939$ ). BMI showed a statistically significant correlation with QRISK in all four age and gender groups, BP was statistically significant for all except females 65-80yrs, and cholesterol was not statistically significant for any of the four groups.

### Odds Ratio and Logistic Regression

Table 6 presents the association between each cardiovascular risk factor and physical activity level. Analysis shows inactive patients were associated with a significantly higher risk of diabetes (odds ratio (OR) = 2.08,  $p=0.002$ ), significantly higher risk of hypertension (OR = 3.12,  $p<0.0005$ ), higher risk of smoking (OR = 1.33,  $p=NS$ ) significantly higher risk of being over weight or obese (OR = 1.987,  $p=0.001$ ), increased risk of high cholesterol (OR = 1.184,  $p=NS$ ) and a significantly greater risk of having a high risk QRISK score (OR = 6.85,  $p<0.0005$ ).



**Figure 7:** Odds ratio for modifiable risk factors of CVD for all active and inactive patients

**Table 3:** Age group characteristics

	Female 40-64 (n=188)	Female 65-80 (n=209)	Male 40-64 (n=215)	Male 65-80 (n=251)
Active n (%)	23.4	10.04	34.4	9.6
Moderately Active n (%)	17.6	7.7	22.3	15
Moderately Inactive n (%)	21.8	8.6	15.3	7.6
Inactive n (%)	37.2	73.66	27.9	67.7
Underweight n (%)	2.1	1.9	0.9	1.6
Normal weight n (%)	31.4	19.1	20	19.9
Overweight n (%)	32.4	38.3	40	47
Obese n (%)	34	40.7	39.1	31.5
Smoker n (%)	12.2	5.3	20.9	12
Ex-smoker n (%)	27.1	39.7	35.8	59
Hypertensive n (%)	39.4	71.8	48.8	68.1
Diabetic n (%)	13.8	17.2	19.5	23.1
Age	49.38 ± 8.6	77.05 ± 4.2	52.58 ± 8.38	71.76 ± 4.42
BMI (kg/m <sup>2</sup> )	28.69 ± 6.88	29.33 ± 5.5	29.28 ± 5.54	28.45 ± 4.57
QRISK score (%)	5.85 ± 6.73	25.42 ± 11.64	13.78 ± 10.82	33.09 ± 10.9
QRISK Active	2.68 ± 3.24	21.85 ± 8.88	10.37 ± 8.31	27.19 ± 7.94
QRISK Mod-Active	5.13 ± 5.04	21.79 ± 9.88	9.84 ± 6.89	28.99 ± 9.12
QRISK Mod-Inactive	5.34 ± 5.07	22.98 ± 8.59	11.16 ± 9.32	29.39 ± 9.16
QRISK Inactive	8.49 ± 8.67	26.57 ± 12.3	22.58 ± 12.03	35.26 ± 11.19
Blood Pressure (mm Hg)	123.84 ± 13.94	136.79 ± 16.63	130.47 ± 14.1	133.96 ± 17.34
Cholesterol (mmol/L)	5.01 ± 1.29	5.42 ± 1.2	5.02 ± 1.12	4.92 ± 3.67
HDL Cholesterol (mmol/L)	1.54 ± 0.5	2.49 ± 10.24	1.26 ± 0.36	2.06 ± 10.59

Logistic Regression was performed to test the effects of diabetes, hypertension, high cholesterol, age and physical activity level on QRISK. The dependant variable (DV) and all independent variables (IV) were categorical with the exception of age and were coded using parameter coding. Results

indicated the three-predictor model provided a statistically significant improvement over the constant-only model,  $\chi^2(3, N=413) = 150.335$ ,  $p < .0005$ . The Nagelkerke  $R^2$  indicated that the model accounted for 28.9% of the total variance and the correct prediction rate was about 69.4%. The Wald tests showed that inactivity, diabetes and hypertension all significantly predicted occurrence of high QRISK. Obesity and smoking both increased odds ratio, with Exp (B) 1.491 and 1.174, neither produced significant increases in risk, although when adjusting for age and gender both were significant. High cholesterol was not a significant predictor of high QRISK even with adjustments for age and gender. Similar to odds ratio, relative risk of high QRISK among patients showed hypertension (RR=1.945, 95% CI: 1.335, 2.834,  $p=.001$ ), diabetes (RR=2.993, 95% CI: 1.806, 4.960,  $p<.0005$ ) and physical inactivity (RR=5.746, 95% CI: 3.696, 8.933,  $p<.0005$ ) all had statistically significant relationships to high QRISK, with overweight and obesity (RR=1.491, 95% CI: .971, 2.291,  $p=.068$ ) and smoking (RR=1.174, 95% CI: .675, 2.043,  $p=.569$ ) increasing risk but not significantly.

## Discussion

The present study demonstrates that physical inactivity accompanies a positive association with several risk factors of CVD. Both men and women who were inactive were at increased risk of diabetes, hypertension, smoking, being overweight or obese, having high cholesterol and producing higher personalised QRISK scores. Few studies have examined the combination of multiple high risk factors of CVD and the accumulative impact these have on personalised CV risk. These results clearly depict a relationship between the negative behaviour of inactivity, combined with other modifiable health behaviours that in turn, can increase personalised QRISK.

## QRISK

As a population the sample's QRISK was  $20.51 \pm 14.70$ , placing the average score in the high-risk category. However, for patients aged 40-64 years QRISK was  $10.08 \pm 9.95$  compared with patients 65-80 years QRISK score of  $35.38 \pm 11.32$ , displaying a statistically significant difference ( $p<.0005$ ). This confirms the relevance of splitting data into age category, in line with Simon *et al.*'s (2010) conclusion of increased cardiovascular risk over 65 years, ensuring further analysis was representative of each group. Gender also proved an important factor, with results showing males produced significantly higher personalised QRISK ( $p<.0005$ ). Higher QRISK in males was persistent in both age groups, despite findings in line with Luke *et al.*'s (2011) conclusions that males are more physically active. This is perhaps accounted for by the prevalence of other negative health behaviours, increasing male risk of additional CVD risk factors examined in the study.

## Gender differences

A larger percentage of males contributed to each negative modifiable risk factor, with significant differences for overweight and obese classifications, current smokers and diabetes. As suggested this increased prevalence is perhaps accountable for the higher QRISK. This is in line with Clarke *et al.*'s (2009) conclusion that baseline differences in risk factors were associated with 10-15 year shorter life expectancy in males over the age of 50 years.

Despite gender differences in individual risk factors, the association between physical inactivity and increased QRISK was apparent throughout all four age and gender groups to varied extents. A significant difference in QRISK scores was present between inactivity and all other activity levels for males and females 40-64 years, yet only significant for males over 65 years. These findings are contradictory to those previous, including Chomistek *et al.*, (2013) who reported that in postmenopausal women, particularly over 70 years, low physical activity augments CVD risk. It is perhaps the case that despite some women over 65 years being more active, these self-reported differences in PA levels are not significant enough to influence other health markers that contribute to QRISK scores and prolonged sedentary behaviours such as sitting can also impact CV risk independent of PA.

### **Physical activity level**

Levels of activity are known to decline after 60 years, which could account for the larger sample size of the inactive group, with a mean age of  $67.57 \pm 9.90$ . In comparison, the more active groups mean ages were 10-years younger, concurring with Plontikoff *et al.*, (2004) that most differences in PA are found within different age groups rather than gender. However, even when accounting for age, similar to findings of Luke *et al.*, (2011) a highly significant association was observed between activity level and all major risk factors, confirming the presence of physiologic consequences of inactivity, as well as negative behaviours, both having implications on CV risk factors. These findings also concur with Chomistek *et al.*, (2013) who reported lower levels of physical activity to be positively associated with current smoking, BMI and depression, suggesting PA may offer increased cognitive and behavioural benefits, directed towards more positive and healthy behaviour choices.

It is unknown if the negative behaviour of being inactive increases individual risk of adopting other negative health behaviours such as smoking, poor diet and excessive alcohol intake, which contribute to the development of conditions such as hypertension and diabetes. However, this data clearly depicts a relationship between inactivity and increased risk. Odds ratios comparing inactive and active patients show that adopting an inactive lifestyle, placed patients at increased risk of all investigated CV risk factors. Although this does not define PA to be the cause of these developments in ill-health, it does show an effect of negative behaviour patterns and it is widely accepted that a conscious choice to regularly exercise, could positively influence adults to adopt other positive health patterns.

### **Physical activity and other CV risk factors**

#### *Diabetes*

A significant difference was found between physical activity levels and the prevalence of diabetes within the population sample, despite only 18% of the sample having diabetes, over 60% of these diabetics were reported as physically inactive. Physical activity is known for its long-term efficacy in reducing CV risk in patients with diabetes (Okada *et al.*, 2010), in addition to preventing the incidence of the disease. As patients with diabetes are known to be at increased risk, preventing the onset of diabetes through PA as a



preventative intervention could consequently reduce risk of CVD. Results clearly endorse these protective mechanisms, showing inactive patients were almost three times as likely to be diabetic and diabetes significantly predicted a high QRISK score, concurring with Dixon *et al.*'s (2013) conclusions that lower levels of PA increase CV markers linked to diabetes, and consequently may increase CV risk.

### *Hypertension*

Treatment for hypertension was extremely prevalent amongst the population studied, with over 50% of all patients on hypertensive medication. There was no significant difference between genders with again over half of males and females hypertensive. There was however, a significant correlation between BP and QRISK and a significant difference between PA groups. As hypertension inferred a significant predictor of high QRISK and those who were inactive were at significantly increased risk of hypertension, a negative association can be assumed between these two risk factors, endorsing PA to be able to produce protective effects on BP and reduce the occurrence of hypertension in patients, again contributing to a reduced personalised QRISK.

### *Smoking*

Similar to the General Practice value of 18.6%, only 12.6% of the samples were current smokers. Prevalence of smoking has declined steadily since the 1970's and when considering 41.6% of patients were ex-smokers, this may underestimate the associations with persistent smoking, compared to never smoking, impacting those ex-smokers whose status for analysis was now non-smoker. This will have implications for results and may account for the non-significant difference between PA groups. Although inactive patients had higher odds of risk, neither this nor logistic regression showed smokers to be at a significantly increased risk of high QRISK. It would perhaps produce different results if those who were ex-smokers were analysed and more detail on smoking habits were known as Clarke *et al.*, (2009) showed cessation of smoking at 60, 50, 40 or 30 years, retrospectively, added about 3, 6, 9 or 10 years of life expectancy when researching cardiovascular risk factors. A significant difference was observed between genders, with higher numbers of males currently smoking. This could perhaps link to males overall higher prevalence of high cholesterol ( $p < .0005$ ) and high QRISK ( $p < .0005$ ). Vigorous efforts have been made to improve levels of smoking, hypercholesterolemia and uncontrolled hypertension to reduce CVD mortality. However, these results clearly demonstrate improvements in healthy lifestyles need to continue to reduce the adverse trends associated between each CV risk factor and physical inactivity.

### *Overweight and obesity*

Despite a well recognised urgency attached to prevention of obesity and age-related weight gains (Caballero, 2007), collectively, the occurrence of overweight and obese patients was not significantly greater in the inactive groups compared with the other three more active groups. These are in line with other studies where a weak negative association has been shown between activity measures, BMI and obesity (Luke *et al.*, 2011). Despite approximately 40% of the population being overweight and of minimal

variance between activity groups, co-occurrence of other risk factors was significantly higher for the inactive groups. In line with previous studies, this could suggest that physical activity has favorable protective effects on the occurrence and development of negative CV and metabolic health markers, independent of weight loss. Positive correlations were found with BMI and QRISK and BMI and age, again concurring with findings that transitions such as retirement may accompany excess weight gain and these can have negative effects on QRISK scores (Plontikoff *et al.*, 2011).

It is worth noting that although numbers of overweight patients were exceptionally high throughout all activity levels, the number of obese patients were significantly higher in the inactive compared with active groups ( $p=.001$ ). With 36.2% of the population obese, compared to the practice value of 11.2% and the local authority profile for Cornwall of 10.7%, this is an extremely high prevalence of obesity within the study sample. From total patients obese, just 13.8% were active compared with 60.3% inactive and despite PA being a significant predictor of obesity, obesity was not a significant predictor of high QRISK, except when adjusting for age and gender. As no significant difference was observed in overweight and obese categories between genders, this can only suggest that age combined with inactivity and obesity is a major contributor to increase QRISK. Whether or not increased activity prevents weight gain is a contentious question with studies and data presenting varied outcomes. However, increased energy expenditure for other protective effects of CV health, in addition to or when exempt from weight loss, in the aging population presents a potentially protective mechanism.

### **Intervention and education**

Findings match those of Wen *et al.*, (2011) in terms of PA's central role in non-communicable diseases and similarly, shows even small increases in PA can be beneficial to CV health, with moderately active groups displaying similar protective effects as active groups. Increases in physical activity, even if not meeting the recommendations, offer the potential to reduce CVD risk substantially, as well as reducing the co-occurrence of other negative risk factors. Health benefits of PA even at moderate levels have been recognized in these findings and encouragement is needed to help currently inactive patients to increase PA behaviours. Patient education programs customized to address unique needs and concerns for specific patients, haven been shown to inflict positive change in a range of health related behaviours (Kreuter & Strecher, 1996). Therefore, knowledge of personalised QRISK, management of specific individual health behaviours and PA interventions combined, may provoke positive effects in risk reduction, as it is suggested that people are more likely to thoughtfully process information when they perceive it to be personally relevant (Bull *et al.*, 1999). If patients can be motivated to make comprehensive changes to lifestyle that are maintainable, equating to overall change to regression effects, then data shows that 40-64 years olds are optimal targets for intervention, aiming to prevent declines in PA. Behaviour change is optimal for longevity and correcting several lifestyle factors simultaneously can produce significant effects. The efficacy of lifestyle programs directed at patients without established CVD but who are at a seemingly high risk, could perhaps offer cost-effective prevention.

In GP practices this potential is only partly fulfilled due to structural, organizational and time restricting barriers. Although health risk assessment tools such as QRISK appear to offer useful ways to identify those at progressively increased risk perhaps due to negative health behaviours, these patients are not flagged or identified until they actually become high risk, unless they are actively seen in GP clinics. Brief interventions in primary care are then perhaps insufficient to achieve and maintain the level of behavioural and physiological changes required to reduced QRISK and prevent development of disease.

### **Strengths and limitations**

A distinct strength of this study was the use of the most recent clinical patient data for all variables and the elimination of self-reported data for each health marker. The precise proportion of adults who fail to meet the current recommendations for PA is hard to quantify, as estimates widely vary depending on data collection method. GPPAQ provided grouped data based on different types of PA including leisure time, occupational and recreational activity, using self-reported intensity and frequency accumulated to produce a score. Even slight differentials in questionnaire response or recall ability would therefore dramatically influence the group each participant are categorised in, consequently effecting size and comparisons between groups and perhaps more quantifiable measure to assess PA would produce more accurate results.

### **Conclusions and recommendations**

This large population study, presents a clear association between physical inactivity and increased QRISK in patients over 40years, in addition to increased risk of specific health risk factors also known to contribute CV risk. As these markers can be linked to negative health behaviours such as poor diet, smoking, excessive alcohol consumption and inactivity, considerable attention directed at strategies to promote appropriate modification of behaviour is vital. GP-based intervention programs offer an opportunity for identification of high-risk patients and this data clearly shows a need for intervention and education to patients who have not yet attained high QRISK Readcodes but are at an increasingly high risk. If these findings were translated into a useful tool to direct patient education routinely offered by GP practices, the potential for substantial change is greater and may produce significant effects. Each patient in the study who had GPPAQ Readcodes recorded would have been notified during consultation of their current activity level. It would be interesting for future studies to investigate if this acknowledgement of current inactivity was enough to prompt behaviour change, or if more detailed and intensive intervention is perhaps required. Combined notification of inactivity and personalised QRISK scores would perhaps increase patients' perceived need to change and is a second area of interest for future study. There is a critical need to better understand the determinants of PA to develop interventions and promote active and healthy lifestyles in older adults and future study should aim to facilitate the delivery of cost-effective methods to prevent inactivity and other negative health

behaviours in the aging population, to counteract increases in QRISK with age.

## **Reference List**

Ahmed, H. M., Blaha, M. J., Nasir, K., Rivera, J. J. & Blumenthal, R. S. (2012). Effects of Physical Activity on Cardiovascular Disease. *The American Journal of Cardiology*. Vol 109: 288-295

Ashenden, R., Silagy, C. & Weller, D. (1997). A Systematic Review of the Effectiveness of Promoting Lifestyle Change in General Practice. *Family Practice*. Vol 14(2): 160-175

Bassuk, S. S. & Manson, J. E. (2005). Epidemiological Evidence for the Role of Physical Activity in Reducing Risk of Type 2 Diabetes and Cardiovascular Disease. *Journal of Applied Physiology*. Vol 99: 1193-1204

Booth, A. O., Nowson, C. A. (2007). Patient Recall of Receiving Lifestyle Advice for Overweight and Hypertension From Their General Practitioner. *BMC Family Practice*. Vol 11(8): 1-7

Brown, R. E., Riddell, M. C., Macpherson, A. K., Canning, K. L. & Kuk, J. L. (2013). The Joint Association of Physical Activity, Blood-Pressure Control, and Pharmacological Treatment of Hypertension for All-Cause Mortality Risk. *American Journal of Hypertension*. Vol 23: 1005-1010

Bull, F. C., Kreuter, M. W., & Scharff, D. P. (1999). Effects of Tailored, Personalized and General Health Messages on Physical Activity. *Patient Education and Counseling*. Vol 36: 181-192

Caballero, B. (2007). The Global Epidemic of Obesity: An Overview. *Epidemiologic Reviews*. Vol 29: 1-5

Chomistek, A. K., Manson, J. E., Stefanick, M. L., Lu, B., Sands-Lincoln, M., Going, S. B., Garcia, L., Allison, M. A., Sims, T. S., LaMonte, M. J., Johnson, K. C. & Eaton, C. B. (2013). Relationship of Sedentary Behavior and Physical Activity to Incident Cardiovascular Disease. *Journal of American College of Cardiology*. Vol 61(23): 2346-2354

Clarke, R., Emberson, J., Fletcher, A., Breeze, E., Marmot, M. & Shipley, M. J. (2009). Life Expectancy in Relation to Cardiovascular Risk Factors: 38 year Follow-up of 19 000 men in the Whitehall Study. *BMJ*. 1-8

Dixon, N. C., Hurst, T. L., Talbot, D. C. S., Tyrrell, R. M. & Thompson, D. (2013). Effects of Short-term Reduced Physical Activity on Cardiovascular Risk Factors in Active Lean and Overweight Middle-aged Men. *Metabolism Clinical and Experimental*. Vol 62: 361-368

Egede, L. E. & Zheng, D. (2002). Modifiable Cardiovascular Risk Factors in Adults with Diabetes. *American Medical Association*. Vol 162: 427-433

Hamer, M. & Stamatakis, E. (2008). The Accumulative Effects of Modifiable Risk Factors on Inflammation and Haemostasis. *Brain, Behavior and Immunity*. Vol 22: 1041-1043

Harris, J. (2008). The Role of Primary GHealth Care in Preventing the Onset of Chronic Disease, With a Particular Focus on the Lifestyle Risk Factors of Obesity, Tobacco and Alcohol. *Centre for Primary Health Care and Equity*. 1-21

HIPA (2013). Health Impact of Physical Inactivity. *Public Health England*. Available at: [http://www.apho.org.uk/addons/\\_122359/atlas.html](http://www.apho.org.uk/addons/_122359/atlas.html) [Accessed 09/12/2013]

Hippisley-Cox, J., Coupland, C., Vinogradova, Y., Robson, J., May, M. & Brindle, P. (2007). Derivation and Validation of QRISK, a New Cardiovascular Disease Risk Score for the United Kingdom: Prospective Open Cohort Study. *BMJ*. 1-12

Hu, F. B., Willett, W. C., Li, T., Stampfer, M. J., Colditz, G. A. & Manson, J. E. (2004). Adiposity as compared with Physical Activity in Predicting Mortality Among Young Women. *The New England Journal of Medicine*. Vol 351(26): 2694-2703

Jousilahti, P., Vartiainen, Tuomilehto, J. & Puska, P. (1999). Sex, Age, Cardiovascular Risk Factors and Coronary Heart Disease: A Prospective Follow-Up of 14 786 Middle-Aged Men and Women in Finland. *Circulation*. Vol 99: 1165-1172

Kreuter, M. W., & Strecher, V. J. (1996). Do Tailored Behaviour Change Messages Enhance the Effectiveness of Health Risk Appraisal? Results from a Randomized Trial. *Health and Education Research*. Vol 11(1): 97-105

Luke, A., Dugas, L. R., Durazo-Arvizu, R. A., Cao, G. & Cooper, R. S. (2011). Assessing Physical Activity and its Relationship to Cardiovascular Risk Factors: NHANES 2003-2006. *BMJ Public Health*. Vol 11(387): 1-12

McNaughton, S. A., Crawford, D., Bull, K. & Salmon, J. (2012). Understanding Determinants of Nutrition, Physical Activity and Quality of Life Among Older Adults: The Wellbeing, Eating and Exercise for a Long Life (WELL) Study. *Health and Quality of Life Outcomes*. Vol 10(109): 1-7

Moe, B., Eilertsen, E. & Nilsen, T. I. L. (2013). The Combined Effect of Leisure-Time Physical Activity and Diabetes on Cardiovascular Mortality: The Nord-Trøndelag Health (HUNT) Cohort Study, Norway. *Diabetes Care*. Vol 36(3): 690-695

Myers, J. (2003). Exercise and Cardiovascular Health. *Circulation*. Vol 107: 1-4

Okada, S., Hiuge, A., Makino, H., Nagumo, A., Takaki, H., Konishi, H., Goto, Y., Yoshimasa, Y. & Miyamoto, Y. (2010). Effect of Exercise Intervention on Endothelial Function and Incidence of Cardiovascular Disease in Patients with Type 2 Diabetes. *Journal of Atherosclerosis and Thrombosis*. Vol 17(8): 828-833

Ornish, D., Brown, S. E., Scherwitz, L. W., Billings, J. H., Armstrong, W. T., Ports, T. A., McLanahan, S. M., Kirkeedie, R. L., Brand, R. J. & Gould, K. L. (1990). Can Lifestyle Changes Reverse Coronary Heart Disease? The Lifestyle Trial. *The Lancet*. Vol 336: 129-133

Plotnikoff, R. C., Mayhew, A., Birkett, N., Loucaides, C. & Fodor, G. (2004). Age, Gender and Urban-Rural Differences in the Correlates of Physical Activity. *Preventative Medicine*. Vol 39: 1115-1125

SEPHO (2013). Cardiovascular Disease Local Authority Health Profile: Cornwall. *South East Public Health Observatory*. Available at: [http://www.sepho.org.uk/NationalCVD/docs/00HE\\_CVD%20Profile.pdf](http://www.sepho.org.uk/NationalCVD/docs/00HE_CVD%20Profile.pdf) [Accessed 12.09.2013]

Simon, C., Everitt, H. & Van-Dorp, F. (2010). *Oxford Handbook of General Practice*. Third Edition. Oxford Uni Press.

Wen, C. P., Wai, J. P. N., Tsai, M. K., Yang, Y. C., Cheng, T. Y. D., Lee, M., Chan, H. T., Tsao, C. K., Tsai, S. P. & Wu, X. (2011). Minimum Amount of Physical Activity for Reduced Mortality and Extended Life Expectancy: A Prospective Cohort Study. *The Lancet*. Vol 378: 1244-1253